AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application:

1. (**Withdrawn**) A hybrid ligand represented by the general formula: R1-Y-R2, wherein:

   (i) R1 represents a first ligand selected from: a steroid, retinoic acid, beta-lactam antibiotic, cannabinoid, nucleic acid, polypeptide, FK506, FK506 derivative, rapamycin, tetracycline, methotrexate, novobiocin, maltose, glutathione, biotin, vitamin D, dexamethasone, estrogen, progesterone, cortisone, testosterone, nickel, 2,4-diaminopteridine or cyclosporin, or a derivative thereof with minor structural modifications;

   (ii) Y represents a polyethylene linker having the general formula $(CH_2\text{-}X\text{-}CH_2)_n$, where X represents O, S, SO, or SO_2, and n is an integer from 2 to 25; and,

   (iii) R2 represents a user-specified second ligand different from R1 selected from: a peptide, nucleic acid, carbohydrate, polysaccharide, lipid, prostaglandin, acyl halide, alcohol, aldehyde, alkane, alkene, alkyne, alkyl, alkyl halide, alkaloid, amine, aromatic hydrocarbon, sulfonate ester, carboxylate acid, aryl halide, ester, phenol, ether, nitrile, carboxylic acid anhydride, amide, quaternary ammonium salt, imine, enamine, amine oxide, cyanohydrin, organocadmium, aldol, organometallic, aromatic hydrocarbon, nucleoside, or a nucleotide.

2. (**Withdrawn**) The hybrid ligand of claim 1, wherein the first ligand binds to a polypeptide.

3. (**Withdrawn**) The hybrid ligand of claim 2, wherein the binding affinity corresponds to a ligand / polypeptide dissociation constant K_D of less than 1 μM.

4. (**Withdrawn**) The hybrid ligand of claim 2, wherein the first ligand is capable of forming a covalent bond with the polypeptide.

5. (**Withdrawn**) The hybrid ligand of claim 1, wherein X is O.

6. (**Withdrawn**) The hybrid ligand of claim 1, wherein Y is $(CH_2\text{-}O\text{-}CH_2)_n$, where n = 2 to 5.

7. (**Withdrawn**) The hybrid ligand of claim 1, wherein R1 is dexamethasone.

8. (**Withdrawn**) The hybrid ligand of claim 1, wherein R1 is methotrexate, a methotrexate derivative, FK506, an FK506 derivative or a 2,4-diaminopteridine derivative.

9. (**Withdrawn**) The hybrid ligand of claim 1, wherein R1 is methotrexate and Y is $(CH_2\text{-}O\text{-}CH_2)_n$, where n = 2 to 5.

10. (**Withdrawn**) The hybrid ligand of claim 1, wherein R2 is a ligand selected from: a compound with a known biological effect, a compound with an unknown mechanism of action, a compound which binds to more than one polypeptide, a drug candidate compound, or a compound that binds to an unknown protein.

11. (**Withdrawn**) The hybrid ligand of claim 1, wherein R2 binds to or inhibits a kinase.

12. (**Withdrawn**) A hybrid ligand represented by the general formula: R1-Y-R2, wherein:

    (i) R1 represents a first ligand selected from: a steroid, retinoic acid, beta-lactam antibiotic, cannabinoid, nucleic acid, polypeptide, FK506, FK506 derivative, rapamycin, tetracycline, methotrexate, novobiocin, maltose, glutathione, biotin, vitamin D, dexamethasone, estrogen, progesterone, cortisone, testosterone, nickel, 2,4-diaminopteridine or cyclosporin, or a derivative thereof with minor structural modifications;

    (ii) Y represents a linker; and,

    (iii) R2 represents a user-specified second ligand different from R1 selected from: a peptide, nucleic acid, carbohydrate, polysaccharide, lipid, prostaglandin, acyl halide, alcohol, aldehyde, alkane, alkene, alkyne, alkyl, alkyl halide, alkaloid, amine, aromatic hydrocarbon, sulfonate ester, carboxylate acid, aryl halide, ester, phenol, ether, nitrile, carboxylic acid anhydride, amide, quaternary ammonium salt, imine, enamine, amine oxide, cyanohydrin, organocadmium, aldol, organometallic, aromatic hydrocarbon, nucleoside, or a nucleotide;

wherein R2 binds to or inhibits a kinase.

13. (**Withdrawn**) The hybrid ligand of claim 12, wherein the kinase is a cyclin dependent kinase.

14. (**Withdrawn**) The hybrid ligand of claim 12, wherein R2 is a ligand selected from Table 2, or a derivative thereof with minor structural modifications.

15. (**Withdrawn**) The hybrid ligand of claim 12 wherein Y represents a polyethylene linker having the general formula $(CH_2\text{-}X\text{-}CH_2)_n$, where X represents O, S, SO, or SO_2, and n is an integer from 2 to 25.

16. (**Withdrawn**) A fusion polypeptide, comprising segments P1, Cub-Z, and RM, in an order wherein Cub-Z is closer to the N-terminus of the fusion polypeptide than RM, wherein

    (i) P1 is a ligand binding polypeptide that binds to a non-peptide ligand of a hybrid ligand, which has the general formula R1-Y-R2, where R1 and R2 are ligands, and Y is a linker,

    (ii) Cub is a carboxy-terminal subdomain of ubiquitin,

    (iii) Z is an amino acid residue,

    (iv) RM is a reporter moiety.

17. (**Withdrawn**) A fusion polypeptide, comprising segments P1 and Nux, wherein

    (i) Nux is the amino-terminal subdomain of a wild-type ubiquitin or a reduced-associating mutant ubiquitin amino-terminal subdomain, and

    (ii) P1 is a ligand binding polypeptide that binds to a non-peptide ligand of a hybrid ligand, which has the general formula R1-Y-R2, where R1 and R2 are ligands, R1 is different from R2, and at least one of R1 and R2 is not a peptide, and Y is a linker.

18. (**Withdrawn**) The fusion polypeptide of claim 16 or 17, wherein the non-peptide ligands are:

a steroid, retinoic acid, beta-lactam antibiotic, cannabinoid, nucleic acid, FK506, FK506 derivative, rapamycin, tetracycline, methotrexate, 2,4-diaminopteridine derivative,

novobiocin, maltose, glutathione, biotin, vitamin D, dexamethasone, estrogen, progesterone, cortisone, testosterone, nickel, cyclosporin, or a derivative thereof with minor structural modifications; or

a carbohydrate, polysaccharide, lipid, prostaglandin, acyl halide, alcohol, aldehyde, alkane, alkene, alkyne, alkyl, alkyl halide, alkaloid, amine, aromatic hydrocarbon, sulfonate ester, carboxylate acid, aryl halide, ester, phenol, ether, nitrile, carboxylic acid anhydride, amide, quaternary ammonium salt, imine, enamine, amine oxide, cyanohydrin, organocadmium, aldol, organometallic, aromatic hydrocarbon, nucleoside, or a nucleotide.

19. **(Withdrawn)** The fusion polypeptide of claim 16, wherein Z is a non-methionine amino acid.

20. **(Withdrawn)** The fusion polypeptide of claim 16, wherein RM is: a polypeptide capable of emitting light upon excitation, a polypeptide with an enzymatic activity, a detectable tag or a transcription factor.

21. **(Withdrawn)** The fusion polypeptide of claim 16, wherein RM is: green fluorescent protein, URA3 or PLV.

22. **(Withdrawn)** A nucleic acid encoding the fusion polypeptide of any one of claims 16 or 17.

23. **(Withdrawn)** A composition, comprising:

(i) a hybrid ligand of the general formula R1-Y-R2, where R1 and R2 are ligands, R1 is different from R2 and at least one of R1 and R2 is not a peptide, Y is a linker; and,

(ii) at least one of two fusion polypeptides comprising:

(a) a first fusion polypeptide comprising segments P2, Cub-Z, and RM, in an order wherein Cub-Z is closer to the N-terminus of the first fusion polypeptide than RM, wherein P2 is a ligand binding polypeptide that may bind to ligand R1 or R2 of the hybrid ligand, Cub is a carboxy-terminal subdomain of ubiquitin and RM is a reporter moiety, and Z is an amino acid residue;

(b) a second fusion polypeptide comprising segments Nux and P1, wherein Nux is the amino-terminal subdomain of a wild-type ubiquitin or a reduced-associating mutant ubiquitin amino-terminal subdomain, and P1 is a ligand binding polypeptide that may bind to ligand R1 or R2 of the hybrid ligand.

24. (**Withdrawn**) A composition, comprising:

(i) a hybrid ligand represented by the general formula: R1-Y-R2, wherein:

(a) R1 represents a first ligand selected from: a steroid, retinoic acid, beta-lactam antibiotic, cannabinoid, nucleic acid, polypeptide, FK506, FK506 derivative, rapamycin, tetracycline, methotrexate, 2,4-diaminopteridine derivative, novobiocin, maltose, glutathione, biotin, vitamin D, dexamethasone, estrogen, progesterone, cortisone, testosterone, nickel, or cyclosporin, or a derivative thereof with minor structural modifications;

(b) Y represents a polyethylene linker having the general formula $(CH_2\text{-}X\text{-}CH_2)_n$, where X represents O, S, SO, or SO_2, and n is an integer from 2 to 25;

(c) R2 represents a user-specified second ligand different from R1 selected from: a peptide, nucleic acid, carbohydrate, polysaccharide, lipid, prostaglandin, acyl halide, alcohol, aldehyde, alkane, alkene, alkyne, alkyl, alkyl halide, alkaloid, amine, aromatic hydrocarbon, sulfonate ester, carboxylate acid, aryl halide, ester, phenol, ether, nitrile, carboxylic acid anhydride, amide, quaternary ammonium salt, imine, enamine, amine oxide, cyanohydrin, organocadmium, aldol, organometallic, aromatic hydrocarbon, nucleoside, or a nucleotide;

(ii) at least one fusion polypeptide selected from:

(a) a first fusion polypeptide comprising: a ligand binding domain P1 and a domain selected from the group consisting of: a DNA

binding domain and a transcriptional activation domain, wherein the ligand binding domain binds the first ligand R1; and,

(b) a second fusion polypeptide comprising: a candidate ligand-binding domain P2 for the user-specified ligand R2 and a domain selected from the group consisting of: a DNA binding domain and a transcriptional activation domain.

wherein one of the first and second fusion polypeptides contains a DNA binding domain and the other fusion polypeptide contains a transcription activation domain;

25. (**Withdrawn**) A composition comprising:

(i) A hybrid ligand represented by the general formula: R1-Y-R2, wherein:

(a) R1 represents a first ligand selected from: a steroid, retinoic acid, beta-lactam antibiotic, cannabinoid, nucleic acid, polypeptide, FK506, FK506 derivative, rapamycin, tetracycline, methotrexate, 2,4-diaminopteridine derivative, novobiocin, maltose, glutathione, biotin, vitamin D, dexamethasone, estrogen, progesterone, cortisone, testosterone, nickel, or cyclosporin or a derivative thereof with minor structural modifications;

(b) Y represents a polyethylene linker having the general formula $(CH_2\text{-}X\text{-}CH_2)_n$, where X represents O, S, SO, or SO2, and n is an integer from 2 to 25;

(c) R2 represents a user-specified second ligand different from R1 selected from: a peptide, nucleic acid, carbohydrate, polysaccharide, lipid, prostaglandin, acyl halide, alcohol, aldehyde, alkane, alkene, alkyne, alkyl, alkyl halide, alkaloid, amine, aromatic hydrocarbon, sulfonate ester, carboxylate acid, aryl halide, ester, phenol, ether, nitrile, carboxylic acid anhydride, amide, quaternary ammonium salt, imine, enamine, amine oxide,

cyanohydrin, organocadmium, aldol, organometallic, aromatic hydrocarbon, nucleoside, or a nucleotide; and

(ii) a fusion polypeptide that includes:

(a) at least one ligand binding domain; and,

(b) a functional domain heterologous to the ligand binding domain which by itself is not capable of inducing or allowing the detection of a detectable event, but which is capable of inducing or allowing the detection of a detectable event when brought into proximity of a second functional domain.

26. (**Withdrawn**) The composition of any one of claims 23 to 25, wherein the composition is a complex.

27. (**Withdrawn**) The composition of any one of claims 23 to 25, wherein the composition is provided in an environment chosen from: a cell, a container, a kit, a solution or a growth medium.

28. (**Original**) A method of identifying a polypeptide sequence that binds to a user-specified ligand comprising:

(i) providing a hybrid ligand having the general formula R1-Y-R2, where R1 is a first ligand, R2 is a user-specified ligand, and Y is a polyethylene linker having the general formula $(CH_2\text{-}X\text{-}CH_2)_n$, where X represents O, S, SO, or SO_2, and n is an integer from 2 to 25;

(ii) introducing the hybrid ligand into a population of cells, each cell containing a hybrid ligand screening system including:

(a) a reporter gene operably linked to a transcriptional regulatory sequence, said regulatory sequence including a DNA sequence which binds to a DNA binding domain;

(b) a first chimeric gene encoding a first fusion polypeptide comprising: a ligand binding domain P1 and a domain selected from a DNA binding domain or a transcriptional activation

domain, wherein the ligand binding domain binds the first ligand R1; and,

(c) a second chimeric gene encoding a second fusion polypeptide comprising: a candidate ligand-binding domain P2 for the user-specified ligand R2 and a domain selected from a DNA binding domain or a transcriptional activation domain;

wherein one of the two fusion polypeptides contains a DNA binding domain and the other fusion polypeptide contains a transcription activation domain;

(iii) allowing the hybrid ligand to bind the ligand binding domain of the first fusion polypeptide through the first ligand R1 and to contact the candidate ligand binding domain of the second fusion polypeptide through the user-specified ligand R2 such that, if R2 binds to the candidate ligand binding domain, an increase in the level of transcription of the reporter gene occurs;

(iv) identifying a positive ligand binding cell in which an increase in the level of transcription of the reporter gene has occurred; and,

(v) identifying the nucleic acid sequence of the second chimeric gene encoding the candidate ligand binding domain that binds to the user-specified ligand R2, thereby identifying a polypeptide sequence that binds to a user-specified ligand.

29. **(Original)** The method of claim 28, wherein the nucleic acid sequence encoding the candidate ligand binding domain polypeptide of the second fusion polypeptide is from a library selected from: a synthetic oligonucleotide library, a cDNA library, a bacterial genomic DNA fragment library, or a eukaryotic genomic DNA fragment library.

30. **(Original)** The method of claim 28, wherein the first ligand R1 of the hybrid ligand binds to the ligand binding domain P1 with a high affinity.

31. **(Original)** The method of claim 30, wherein the binding affinity corresponds to a ligand / ligand binding protein dissociation constant K_D of less than 1 μM.

32. (**Withdrawn**) The method of claim 28, wherein the first ligand is capable of forming a covalent bond with the ligand binding domain P1.

33. (**Original**) The method of claim 28, wherein X is O.

34. (**Original**) The method of claim 28, wherein Y is $(CH_2\text{-}O\text{-}CH_2)_n$, where n = 2 to 5.

35. (**Original**) The method of claim 28, wherein R1 is methotrexate, and Y is $(CH_2\text{-}O\text{-}CH_2)_n$, n = 2 to 5.

36. (**Original**) The method of claim 28, wherein the reporter gene is selected from: HIS3, LEU2, TRP2, TRP1, ADE2, LYS2, URA3, CYH1, CAN1, *lacZ*, gfp or CAT.

37. (**Original**) The method of claim 28, wherein R2 binds to or inhibits a kinase.

38. (**Currently Amended**) A method of identifying a polypeptide sequence that binds to a user-specified ligand comprising:

(i) providing a hybrid ligand having the general formula R1-Y-R2, where R1 is a first ligand, R2 is a user-specified ligand different from R1, at least one of R1 and R2 is not a peptide, Y is a linker, and wherein [[R1]] R2 binds to or inhibits a kinase;

(ii) introducing the hybrid ligand into a population of cells, each cell containing a hybrid ligand screening system including:

(a) a reporter gene operably linked to a transcriptional regulatory sequence, said regulatory sequence including a DNA sequence which binds to a DNA binding domain;

(b) a first chimeric gene encoding a first fusion polypeptide comprising: a ligand binding domain and a domain selected from the DNA binding domain or a transcriptional activation domain, wherein the ligand binding domain binds the first ligand R1; and,

(c) a second chimeric gene encoding a second fusion polypeptide comprising: a candidate ligand-binding domain for the user-specified ligand R2 and a domain selected from the DNA binding domain or the transcription activation domain;

wherein one of the two fusion polypeptides contains a DNA binding domain and the other fusion polypeptide contains a transcription activation domain;

(iii) allowing the hybrid ligand to bind the ligand binding domain of the first fusion polypeptide through the first ligand R1 and to contact the candidate ligand binding domain of the second fusion polypeptide through the user-specified ligand R2 such that, if R2 binds to the candidate ligand binding domain, an increase in the level of transcription of the reporter gene occurs;

(iv) identifying a positive ligand binding cell in which an increase in the level of transcription of the reporter gene has occurred; and,

(v) identifying the nucleic acid sequence of the second chimeric gene encoding the candidate ligand binding domain that binds to the user-specified ligand R2, thereby identifying a polypeptide sequence that binds to a user-specified ligand.

39. (**Original**) The method of claim 38, wherein the kinase is a cyclin dependent kinase.

40. (**Original**) The method of claim 38, wherein R2 is a compound selected from Table 2.

41. (**Original**) The method of claim 38, wherein Y is $(CH_2\text{-}X\text{-}CH_2)_n$, n = 2 to 25.

42. (**Currently Amended**) The method of claim 38, wherein R1 represents a first ligand selected from: a steroid, retinoic acid, beta-lactam antibiotic, cannabinoid, nucleic acid, polypeptide, FK506, FK506 derivative, rapamycin, tetracycline, methotrexate, novobiocin, maltose, glutathione, biotin, vitamin D, dexamethasone, estrogen, progesterone, cortisone, testosterone, nickel, 2,4-diaminopteridine ~~derivative~~ or cyclosporin, or a derivative thereof ~~with minor structural modifications~~ having one or more structural modifications but sharing an effective binding moiety therewith that retains ligand binding domain-binding activity.

43. (**Withdrawn**) A method of determining whether a polypeptide P2 and a ligand R2 bind to each other comprising:

(i) translationally providing a first ligand-binding polypeptide comprising segments P1, Cub-Z, and RM, in an order wherein Cub-Z is closer to the N-terminus of the first ligand-binding polypeptide than RM, and a second ligand-binding polypeptide comprising segments Nux and P2, wherein P1 and P2 are polypeptides, Nux is the amino-terminal subdomain of a wild-type ubiquitin or a reduced-associating mutant ubiquitin amino-terminal subdomain, Cub is the carboxy-terminal subdomain of a wild-type ubiquitin, Z is an amino acid residue and RM is a reporter moiety;

(ii) providing a hybrid ligand represented by the general formula: R1-Y-R2, wherein R1 is a first ligand that binds the first ligand-binding polypeptide at P1, R2 is a second ligand different from R1, at least one of R1 and R2 is not a peptide, and Y is a linker;

(iii) allowing the hybrid ligand to contact the first and second ligand-binding polypeptides;

(iv) detecting the degree of cleavage by a ubiquitin-specific protease (UBP) of the first ligand-binding polypeptide between Cub and Z, wherein an increase of cleavage is indicative of polypeptide P2 – ligand R2 binding.

44. (**Withdrawn**) A method of determining whether a polypeptide P1 and a ligand R1 bind to each other comprising:

(i) translationally providing a first ligand-binding polypeptide comprising segments P1, Cub-Z, and RM, in an order wherein Cub-Z is closer to the N-terminus of the first ligand-binding polypeptide than RM, and a second ligand-binding polypeptide comprising segments Nux and P2, wherein P1 and P2 are polypeptides, Nux is the amino-terminal subdomain of a wild-type ubiquitin or a reduced-associating mutant ubiquitin amino-terminal subdomain, Cub is the carboxy-terminal subdomain of a wild-type ubiquitin, Z is an amino acid residue and RM is a reporter moiety;

(ii) providing a hybrid ligand represented by the general formula: R1-Y-R2, wherein R1 is a first ligand, R2 is a second ligand different from R1 that

binds the second ligand-binding polypeptide at P2, at least one of R1 and R2 is not a peptide, and Y is a linker;

(iii) allowing the hybrid ligand to contact the first and second ligand-binding polypeptides;

(iv) detecting the degree of cleavage by a ubiquitin-specific protease (UBP) of the first ligand-binding polypeptide between Cub and Z, wherein an increase of cleavage is indicative of protein P1 – ligand R1 binding.

45. (**Withdrawn**) The method of claim 43 or 44, wherein said method involves the use of a cell providing an N-end rule degradation system.

46. (**Original**) A method of inducing or allowing the detection of a biologically detectable event, comprising:

(i) providing at least one cell comprising at least one nucleic acid sequence encoding a fusion polypeptide that includes:

(a) at least one ligand binding domain; and,

(b) a functional domain which by itself is not capable of inducing or allowing the detection of the detectable event;

(ii) providing a hybrid ligand of the general formula R1-Y-R2, wherein R1 is different from R2, at least one of R1 and R2 is not a peptide, R1 or R2 represents a ligand that binds to said ligand binding domain; Y represents a polyethylene linker having the general formula $(CH_2\text{-}X\text{-}CH_2)_n$, where X represents O, S, SO, or SO_2, and n is an integer from 2 to 25; and wherein the binding of said hybrid ligand to said ligand binding domain brings the first functional domain into proximity of a second functional domain, thereby inducing or allowing the detection of the detectable event; and,

(iii) exposing said at least one cell to an effective amount of said hybrid ligand to bring the first functional domain into proximity of a second functional domain;

thereby inducing or allowing the detection of the biologically detectable event.

47. (**Withdrawn**) A method of identifying a ligand of a user-specified polypeptide, comprising:

(i) providing at least one candidate hybrid ligand having the general formula R1-Y-R2, where R1 is a first ligand, R2 is a candidate ligand, and Y is a polyethylene linker having the general formula $(CH_2\text{-}X\text{-}CH_2)_n$, where X represents O, S, SO, or SO_2, and n is an integer from 2 to 25;

(ii) introducing the candidate hybrid ligand into at least one cell which contains a hybrid ligand screening system including:

(a) a reporter gene operably linked to a transcriptional regulatory sequence, said regulatory sequence including a DNA sequence which binds to a DNA binding domain;

(b) a first chimeric gene encoding a first fusion polypeptide comprising: a ligand binding domain and a domain selected from: a DNA binding domain or a transcriptional activation domain, wherein the ligand binding domain binds the first ligand R1; and,

(c) a second chimeric gene encoding a second fusion polypeptide comprising: a user-specified ligand-binding domain for the candidate ligand R2 and a domain selected from: a DNA binding domain or a transcription activation domain;

wherein one of the two fusion polypeptides contains a DNA binding domain and the other fusion polypeptide contains a transcription activation domain;

(iii) allowing the candidate hybrid ligand to bind the ligand binding domain of the first fusion polypeptide through the first ligand R1 and to contact the user-specified ligand binding domain of the second fusion polypeptide through the candidate ligand R2 such that, if the user-specified ligand binding domain binds to the candidate ligand R2, an increase in the level of transcription of the reporter gene occurs;

(iv) identifying the candidate hybrid ligand which causes an increase in the level of transcription of the reporter gene in the cell, thereby identifying the candidate ligand on the candidate hybrid ligand as a ligand for the user-specified polypeptide.

48. (**Currently Amended**) A method to investigate the structure activity relationship of a ligand to a ligand binding domain comprising:

(i) providing a hybrid ligand R1-Y-R2, wherein

(a) R1 represents a first ligand selected from: a steroid, retinoic acid, beta-lactam antibiotic, cannabinoid, nucleic acid, polypeptide, FK506, FK506 derivative, rapamycin, tetracycline, methotrexate, novobiocin, maltose, glutathione, biotin, vitamin D, dexamethasone, estrogen, progesterone, cortisone, testosterone, nickel, 2,4-diaminopteridine ~~derivative~~ or cyclosporin or a derivative thereof ~~with minor structural modifications~~ having one or more structural modifications but sharing an effective binding moiety therewith that retains ligand binding domain-binding activity;

(b) Y represents a polyethylene linker having the general formula $(CH_2\text{-}X\text{-}CH_2)_n$, where X represents O, S, SO, or SO_2, and n is an integer from 2 to 25; and,

(c) R2 represents a user-specified second ligand which is different from R1 and is selected from: a peptide, nucleic acid, carbohydrate, polysaccharide, lipid, prostaglandin, acyl halide, alcohol, aldehyde, alkane, alkene, alkyne, alkyl, alkyl halide, alkaloid, amine, aromatic hydrocarbon, sulfonate ester, carboxylate acid, aryl halide, ester, phenol, ether, nitrile, carboxylic acid anhydride, amide, quaternary ammonium salt, imine, enamine, amine oxide, cyanohydrin, organocadmium, aldol, organometallic, aromatic hydrocarbon, nucleoside, a nucleotide, or a small molecule;

(ii) providing cells comprising a fusion protein that includes:

(a) at least one ligand binding domain; and,

(b) a functional domain heterologous to the ligand binding domain which by itself is not capable of inducing or allowing the detection of a detectable event, but which is capable of inducing or allowing the detection of a detectable event when brought into proximity of a second functional domain;

wherein either a plurality of hybrid ligands comprising structural variants of said second ligand R2 is provided in step (i), or a plurality of fusion proteins comprising structural variants of said ligand binding domain is provided in step (ii);

(iii) exposing said cells comprising each fusion protein to an effective amount of each hybrid ligand such that the first functional domain may be brought into proximity of a second functional domain thereby inducing or allowing the detection of a detectable event;

(iv) measuring the presence, amount or activity of any detectable event so induced or allowed in step (iii), thereby investigating the structure activity relationship between said second ligand and the ligand binding domain.

49. (**Original**) The method of claim 48, wherein said first functional domain of (b) is chosen from: a DNA binding domain, a transcription activation domain, a carboxy-terminal subdomain of a wild-type ubiquitin, an amino-terminal subdomain of a ubiquitin or a reduced-associating mutant ubiquitin amino-terminal subdomain.

50. (**Original**) The method of any one of claims 28 or 38, further comprising determining the binding affinity of the hybrid ligand to the ligand binding domains P1 and/or P2.

51. (**Original**) The method of claim 50, wherein the determination of the binding affinity is performed by surface plasmon resonance.

52. (**Original**) The method of claim 28 or 38, further comprising determining the effects of the hybrid ligand that are independent of the formation of a trimeric complex comprising the hybrid ligand, P1 and P2.

53. (**Previously Presented**) The method of claim 28 or 38, further comprising the step of: performing at least one additional separate method to confirm that the transcription of the reporter gene is dependent on the presence of the hybrid ligand and the ligand binding domains P1 and P2.

54. (**Original**) The method of claim 53 wherein said additional separate method is selected from: a halo growth assay method, a microtiter plate growth assay, or a fluorescence detection growth assay.

55. (**Original**) The method of claim 53 wherein said additional separate method is individually conducted on greater than about 10, 100, 1000 or 10000 different positive ligand binding cell-types identified in step (iv).

56. (**Withdrawn**) A method to identify a hybrid ligand having the general structure R1-Y-R2 suitable for an *in-vivo* assay, wherein said assay involves:

(i) the use of a hybrid ligand, and

(ii) of at least one fusion polypeptide that includes:

(a) at least one ligand binding domain P; and,

(b) a functional domain which by itself is not capable of inducing or allowing the detection of the detectable event;

and wherein said method involves the steps of:

(iii) synthesizing a plurality of hybrid ligands R1-Y-R2 differing by a plurality of different linkers Y, wherein R1 and R2 are different, and at least one of R1 and R2 is not a peptide; and

(iv) testing each hybrid ligand in said plurality of hybrid ligands individually for efficacy in inducing or allowing the detection of the detectable event; and

(v) selecting a hybrid ligand with a particular linker that possesses suitable efficacy in inducing or allowing the detection of the detectable event.

57. (**Withdrawn**) The method of claim 56 wherein said linker has the general structure $(CH_2\text{-}X\text{-}CH_2)_n$, where X represents O, S, SO, or SO_2, and n is an integer from 2 to 25, and the plurality of linkers differ in n.

58. (**Withdrawn**) The method of claim 56 wherein R1 represents a first ligand selected from: steroid, retinoic acid, beta-lactam antibiotic, cannabinoid, nucleic acid, polypeptide, FK506, FK506 derivative, rapamycin, tetracycline, methotrexate, novobiocin, maltose, glutathione, biotin, vitamin D, dexamethasone, estrogen, progesterone, cortisone, testosterone, nickel, 2,4-diaminopteridine derivative or cyclosporin, or a derivative thereof with minor modifications.

59. (**Withdrawn**) A kit comprising:

at least one polynucleotide including a DNA fragment linked to a coding sequence for a functional domain heterologous to the DNA fragment which by itself is not capable of inducing or allowing the detection of a detectable event, but which is capable of inducing or allowing the detection of a detectable event when brought into proximity of a second functional domain;

and further comprising instructions

(i) to synthesize a hybrid ligand of general structure R1-Y-R2, and

(ii) to clone a ligand binding domain into the polynucleotide, and

(iii) to test the binding between the hybrid ligand and the ligand binding domain,

wherein R2 is different from R1, one of R1 and R2 is a non-peptide ligand, and wherein one of R1 and R2 binds to or inhibits a kinase.

60. (**Withdrawn**) A kit comprising

at least one polynucleotide including a DNA fragment linked to a coding sequence for a functional domain heterologous to the DNA fragment which by itself is not capable of inducing or allowing the detection of a detectable event, but which is capable of inducing or allowing the detection of a detectable event when brought into proximity of a second functional domain;

and further comprising instructions

(i) to synthesize a hybrid ligand of general structure R1-Y-R2, and

(ii) to clone a ligand binding domain into the polynucleotide, and

(iii) to test the binding between the hybrid ligand and the ligand binding domain,

wherein R2 is different from R1, one of R1 and R2 is a non-peptide ligand, and wherein Y is of the general structure $(CH_2\text{-}X\text{-}CH_2)_n$, where X represents O, S, SO, or SO_2, and n is an integer from 2 to 25.

61. (**Withdrawn**) A kit comprising

at least one polynucleotide including a DNA fragment linked to a coding sequence for a functional domain heterologous to the DNA fragment which by itself is not capable of inducing or allowing the detection of a detectable event, but which is capable of inducing or allowing the detection of a detectable event when brought into proximity of a second functional domain;

and further comprising instructions

(i) to synthesize a hybrid ligand of general structure R1-Y-R2, and

(ii) to clone a ligand binding domain into the polynucleotide, and

(iii) to test the binding between the hybrid ligand and the ligand binding domain,

wherein R2 is different from R1, one of R1 and R2 is a non-peptide ligand, and wherein the functional domain is a carboxy-terminal subdomain of ubiquitin or an amino-terminal subdomain of ubiquitin.

62. (**Withdrawn**) A kit comprising:

(i) a compound of general structure R1-Y-L, wherein Y is of the general structure $(CH_2\text{-}X\text{-}CH_2)_n$ and L is a chemical group that is easily substituted by a different chemical group, and

(ii) instructions to use the compound for the synthesis of a hybrid ligand R1-Y-R2 where R1 is different from R2, and at least one of R1 and R2 is not a peptide.

63. (**Original**) A method of doing business comprising:

the identification of polypeptides binding to a hybrid ligand of general formula R1-Y-R2, wherein Y is of the general structure $(CH_2\text{-}X\text{-}CH_2)_n$, R1 is different from R2, and at least one of R1 and R2 is not a peptide, X = O, S, SO or SO_2, and wherein said polypeptides were previously not known to bind to such hybrid ligand, and

providing access to data, nucleic acids or polypeptides obtained from such identification to another party for consideration.

64. (**Canceled**)

65. (**Withdrawn**) A method of doing business comprising:

the identification of at least one ligand binding to a user-specified polypeptide by using a plurality of hybrid ligands of general formula R1-Y-R2 differing in at least one of R1 and R2, wherein R1 and R2 are ligands, R1 is different from R2, at least one of R1 and R2 is not a peptide, Y is of the general structure $(CH_2\text{-}X\text{-}CH_2)_n$, X = O, S, SO or SO_2, and wherein said ligands were previously not known to bind to such polypeptide, and

providing access to data and ligands obtained from such identification to another party for consideration.

66. (**Canceled**)